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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/555,674	08/03/00	GABIZON	A 9325-0007.10

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EXAMINER	
GUTTMAN,H	
ART UNIT	**PAPER NUMBER**
1651	7

DATE MAILED: 10/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/555,674	GABIZON ET AL.	
	Examiner	Art Unit	
	Harry J Guttman	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-30 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☒ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Claims 1-30 are presented for examination on the merits.

Specification

The use of the trademark DOXIL® and STEALTH® has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology at the first instance.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

It is requested that the first line of the first page of the specification indicate that the instant application is a 371 of the earlier filed PCT application, as follows.

This application is a 371 of PCT/IL98/00586, filed 01-Dec-1998, which claims priority to US Provisional application Serial No. 60/067,697, filed 04-Dec-1997.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 14, applicant needs to specify clearly what is being administered. For example, are the drugs encapsulated together in the same liposome or in encapsulated separately in different liposomes?

In claims 2, 15 and 24, applicant needs to further define what "individually" means. Does "individually" refer to administration one after the other, or administration one without the other, or some other method of administration?

In claims 6, 12, 16, and 26 the Markush groups should be correctly phrased. For example, "is selected from" could be replaced with "is selected from the group consisting of".

Claim 5 recites the limitation "vesicle" in line 1. There is insufficient antecedent basis for this limitation in the claim.

In claims 13 and 22, the use of the word "follows" does not clearly indicate the amount of time between administrations.

The term "about 1-10" in claims 3, 5, 14 and 25 is a relative term which renders the claim indefinite. The term "about 1-10" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The amount of mole percent should be specified using either a range or a definite relative term (for example, "about").

The term "analog" in claims 8 and 19 is a relative term which renders the claim indefinite. The term "analog" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

"To describe physical or other properties of material by mere use of **trademark** is objectionable since it has tendency to make trademark descriptive of product rather than leaving trademark to serve its traditional purpose which is to identify product's source of origin". The issue involved the use of the Trademark **Hypalon** in the claims which Appellants have argued to be within the guidelines of M.P.E.P. 608.01 (v) if the meaning of the trademark is well known and satisfactorily defined in the literature. Copies of articles were submitted. No rejection was made based on first paragraph of 35 USC 112 which was correct but the rejection was on second paragraph which was considered to be correct by the board. "A patent applicant has an obligation that is

imposed by 35 USC 112, second paragraph, to employ claim terminology which is definitive of what the public is not free to use, and use of a trademark in the manner employed by appellant has resulted in claims which fail to meet this obligation in our opinion.: see **Ex parte Simpson and Roberts** 218 USPQ 1020.

As such, claims 9, 18, and 28 are rejected under 35 U.S.C. 112, second paragraph, because the use of the Trademark DOXIL® is improper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 10, 11, 13, 23, 24, 29 and 30 are rejected under 35 U.S.C. 102(a) as being anticipated by Kedar et al., (1997). Claims 1, 2 10, 11, and 13 are drawn to antitumor therapy using a combination of a liposome-encapsulated chemotherapeutic drug and of a liposome-encapsulated IL-2. Claims 23, 24, 29, and 30 are drawn to a composition comprising a liposome-encapsulated chemotherapeutic drug and liposome-encapsulated IL-2.

Kedar et al. discloses a "highly efficacious" eradication of tumors comprising a liposome-encapsulated chemotherapeutic drug and liposome-encapsulated IL-2.

Claims 1, 2, 4, 6, 7, 9-13, 23, 24, and 26-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Fondy et al. (WO90/13293). Claims 1, 2, 4, 6, 7, and 9-13 are drawn to antitumor therapy using a combination of a liposome-encapsulated chemotherapeutic drug and of a liposome-encapsulated IL-2. Claims 23, 24, and 26-30 are drawn to a composition comprising a liposome-encapsulated chemotherapeutic drug and liposome-encapsulated IL-2.

On page 21, Fondy et al. disclose IL-2 formulated with cytochalasin using liposomes, which can be further administered with doxorubicin with or without liposomes.

Claims 1-7, 9-18, 20-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Kedar et al (1993). Claims 1-7, 9-18, 20-30 are drawn to antitumor therapy using a combination of a liposome-encapsulated chemotherapeutic drug (dependent to doxorubicin) and of a liposome-encapsulated cytokine (dependent to IL-2), with and without derivatization of the liposome head group by PEG, and composition thereof. Kedar et al. disclose an anti-tumor therapy using encapsulated IL-2 and doxorubicin using cholesterol and PEG1900-DSPE.

Claims 1-7, 9, 10, 12-18, 20, and 22-29 are rejected under 35 U.S.C. 102(a) as being anticipated by ten Hagen et al. (1997). Claims 1-7, 9, 10, 12-18, 20, and 22-29 are drawn to antitumor therapy using a combination of a liposome-encapsulated chemotherapeutic drug (dependent to doxorubicin) and of a liposome-encapsulated cytokine (dependent to TNF-α), with and without derivatization of the liposome head group by PEG, and composition thereof. Ten Hagen et al. disclose an antitumor therapy using Stealth liposome (which have PEG-derivatized lipid head groups)-encapsulated doxorubicin and Stealth liposome-encapsulated TNF-α.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al. (1993) in view of Poirot et al. (1996) and the Merk Index (10^{th} ed.). Claims 8 and 19 are drawn to the use of camptothecin as the chemotherapeutic agent in the invention.

Kedar et al. disclose an anti-tumor therapy using encapsulated IL-2 (cytokine) and doxorubicin (chemotherapeutic agent) using cholesterol and PEG1900-DSPE. Kedar et al. do not disclose the use of camptothecin as the chemotherapeutic agent.

The Merk index discloses that camptothecin (1714) exibits anti-tumor activities.

Poirot et al. disclose the use liposome-encapsulated camptothecin in cytotoxicity assays of KB cells. Poirot et al. discuss that the use of liposomes as a delivery system for camptothecin is logical since it is poorly soluble in water and the liposomes protect camptothecin integrity while in circulation.

One of ordinary skill in the art would have motivated to use camptothecin as a choice of chemotherapeutic agent in the liposome-encaspulated IL-2, chemotherapeutic agent used by Kedar et al., since liposome-encapsulated camptothecin was known as an effective cytotoxin against KB cells and was known as an anti-tumor agent.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references, especially in the absence of evidence to the contrary.

Claims 8 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al. (1993) in view of Burke (US 5552156). Claims 8 and 19 are drawn to the use of camptothecin and camptothecin analogs as the chemotherapeutic agent in the invention.

Kedar et al. disclose an anti-tumor therapy using encapsulated IL-2 (cytokine) and doxorubicin (chemotherapeutic agent) using cholesterol and PEG1900-DSPE. Kedar et al. do not disclose the use of camptothecin or camptothecin analogs as the chemotherapeutic agent.

Burke discloses (a) camptothecin and camptothecin-like drugs as having anti-tumor activity (col 5 and Table I) (b) a variety of lipids, including PEG-derivatized lipid head groups, to be used to encapsulate camptothecin and camptothecin-like drugs (col 6), (c) studies of camptothecin and camptothecin-like drugs associated with liposomes (example 10 and Tables II-V), and (d) the statement that camptothecin and camptothecin-like drugs in liposomes can be used clinically for anti-tumor activities (col 21, lines 51-57, and claim 17)

One of ordinary skill in the art would have motivated to use camptothecin or the camptothecin-like drugs as a choice of chemotherapeutic agent in the liposome-encaspulated IL-2, chemotherapeutic agent used by Kedar et al., since liposome-

encapsulated camptothecin and the camptothecin-like drugs were known as an anti-tumor agent.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references, especially in the absence of evidence to the contrary.

Claims 8 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kedar et al. (1993) in view of Chow et al. (1997). Claims 8 and 19 are drawn to the use of camptothecin and camptothecin analogs as the chemotherapeutic agent in the invention.

Kedar et al. disclose an anti-tumor therapy using encapsulated IL-2 (cytokine) and doxorubicin (chemotherapeutic agent) using cholesterol and PEG1900-DSPE. Kedar et al. do not disclose the use of camptothecin or camptothecin analogs as the chemotherapeutic agent.

Chow et al. disclose camptothecin and 9-nitro-camptothecin encapsulated in liposomes containing DPPC and cholesterol, and their effective use in anti-tumor therapy.

One of ordinary skill in the art would have motivated to use camptothecin or the camptothecin analog as a choice of chemotherapeutic agent in the liposome-

encaspulated IL-2, chemotherapeutic agent used by Kedar et al., since liposome-encapsulated camptothecin and 9-nitro-camptothecin were known as effective anti-tumor agents.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references, especially in the absence of evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication should be directed to Harry J. Guttman, Ph.D. at telephone number (703) 305-0159. The examiner can normally be reached during the hours of 08:00 to 16:30 Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, a message may be left on the voice mail. The fax number for Art Unit 1651 is (703) 308-4242 or 305-3014. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. My supervisor, Michael Wityshyn, may be contacted at (703) 308-4743.

All internet e-mail communications will be made of record in the application file. PTO employees will not communicate with applicant via internet e-mail where sensitive data will be exchanged or where there exists a possibility that sensitive data could be identified or exchanged unless there is of record an express waiver of the confidentiality requirements of 35 U.S.C. 122 by the applicant. See the Interim Internet Usage Policy published in the Patent and Trademark Office Official Gazette on 25 February 1997 at 1195 OG 89.

H.J.G. 20 October 2000

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